Ruthenium-Catalyzed One-Pot β-Alkylation of Secondary Alcohols with Primary Alcohols

Chan Sik Cho*,†

Research Institute of Industrial Technology, Kyungpook National University, Taegu 702-701, Korea

Bok Tae Kim, Hong-Seok Kim, Tae-Jeong Kim, and Sang Chul Shim*

Department of Industrial Chemistry, College of Engineering, Kyungpook National University, Taegu 702-701, Korea

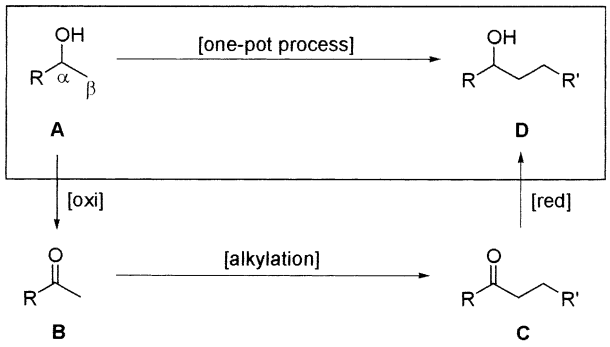
Received April 25, 2003

Summary: *Secondary alcohols (carbinols) react with primary alcohols in dioxane at 80 °C in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$ and KOH along with a sacrificial hydrogen acceptor to afford the corresponding coupled secondary alcohols. The reaction is applicable to a wide range of aryl methyl, alkyl methyl, and cyclic carbinols, and with alkyl methyl carbinols, the alkylation took place exclusively at the less-hindered methyl position over β-methylene and -methine.*

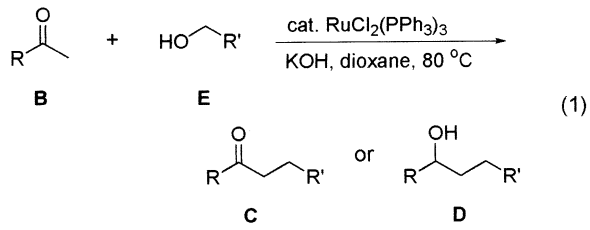
Introduction

Many unit organic reactions have been developed to give high efficiency and convenience of reaction.[1] In connection with this report, as shown in Scheme 1, β-alkylation of secondary alcohol **A** (carbon β-alkylation to the oxygen atom of **A**) generally can be accomplished via several step-by-step unit transformations such as oxidation of secondary alcohol **A** to ketone **B** (**A** → **B**),[2] an appropriate alkylation (**B** → **C**),[3] and reduction of alkylated ketone **C** to alkylated secondary alcohol **D** (**C** → **D**).[4] However, a one-pot process for β-alkylation of **A** (**A** → **D**) without such preconversions is desirable from an organic synthetic point of view. During the course of our ongoing studies on ruthenium-catalyzed organic reactions,[5−8] we found an unusual type of ruthenium-catalyzed transfer hydrogenation of ketones

Scheme 1



B by primary alcohols **E** accompanied by carbon−carbon coupling under KOH (eq 1).[9,10] Tuning the molar ratio



of **E** to **B** was crucial for preferential formation of the alkylated ketone **C**[9b] or the unconventional transfer-hydrogenated secondary alcohol **D**.[9a] It was also suggested that the reaction proceeds via an intrinsic ruthenium-catalyzed redox shuttle between alcohols and

† E-mail: cscho@knu.ac.kr. Fax: (+82)53-950-6594.

(1) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989.

(2) Hudlický, M. *Oxidations in Organic Chemistry*; American Chemical Society: Washington, DC, 1990.

(3) Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 3, pp 1−63.

(4) Hudlický, M. *Reductions in Organic Chemistry*; American Chemical Society: Washington, DC, 1986.

(5) (a) Cho, C. S.; Lim, H. K.; Shim, S. C.; Kim, T. J.; Choi, H.-J. *Chem. Commun.* **1998**, 995. (b) Cho, C. S.; Kim, J. H.; Shim, S. C. *Tetrahedron Lett.* **2000**, *41*, 1811. (c) Cho, C. S.; Kim, J. H.; Kim, T.-J.; Shim, S. C. *Tetrahedron* **2001**, *57*, 3321. (d) Cho, C. S.; Kim, J. H.; Choi, H.-J.; Kim, T.-J.; Shim, S. C. *Tetrahedron Lett.* **2003**, *44*, 2975.

(6) (a) Cho, C. S.; Oh, B. H.; Shim, S. C. *Tetrahedron Lett.* **1999**, *40*, 1499. (b) Cho, C. S.; Kim, J. S.; Oh, B. H.; Kim, T.-J.; Shim, S. C. *Tetrahedron* **2000**, *56*, 7747. (c) Cho, C. S.; Oh, B. H.; Kim, J. S.; Kim, T.-J.; Shim, S. C. *Chem. Commun.* **2000**, 1885. (d) Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *Chem. Commun.* **2001**, 2576. (e) Cho, C. S.; Kim, T. K.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *J. Organomet. Chem.* **2002**, *650*, 65.

(7) Cho, C. S.; Kim, B. T.; Lee, M. J.; Kim, T.-J.; Shim, S. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 958.

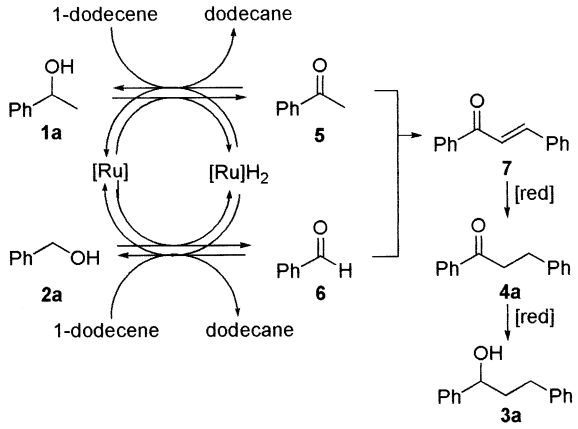
(8) For an excellent review on ruthenium-catalyzed organic reactions: Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599.

(9) (a) For instance, treatment of acetophenone with 3 equiv of benzyl alcohol under the standard set of reaction conditions, $RuCl_2(PPh_3)_3$ (5 mol %)/KOH (3 equiv)/dioxane/80 °C/20 h, afforded 1,3-diphenylpropan-1-ol and 1,3-diphenylpropan-1-one in 77% and 3% isolated yields, respectively: Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *J. Org. Chem.* **2001**, *66*, 9020. (b) For instance, treatment of equimolar amounts of acetophenone and benzyl alcohol under $RuCl_2(PPh_3)_3$ (2 mol %)/KOH (1 equiv)/1-dodecene (1 equiv)/dioxane/80 °C/20 h gave 1,3-diphenylpropan-1-one and 1,3-diphenylpropan-1-ol in 82% and 2% isolated yields, respectively. On the other hand, when the reaction was carried out in the absence of 1-dodecene, 1,3-diphenylpropan-1-one was formed in 70% yield along with a considerable amount of 1,3-diphenylpropan-1-ol (14%): Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *Tetrahedron Lett.* **2002**, *43*, 7987.

(10) For recent reviews on transition-metal-catalyzed transfer hydrogenations: (a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051. (b) Bäckvall, J.-E.; Chowdhury, R. L.; Karlsson, U.; Wang, G. In *Perspectives in Coordination Chemistry*; Williams, A. F., Floriani, C., Merbach, A. E., Eds.; VCH: New York, 1992; pp 463−486. (c) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (d) Palmer, M.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045.

10.1021/om030307h CCC: $25.00
Publication on Web 07/19/2003

Scheme 2



carbonyl compounds.[10] Prompted by these findings, we have directed our attention to the present work. Herein we report an unprecedented one-pot procedure for β-alkylation of secondary alcohols with primary alcohols in the presence of a ruthenium catalyst along with a base and a sacrificial hydrogen acceptor.

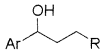
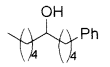
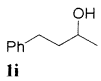
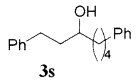
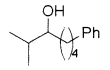
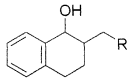
Results and Discussion

Treatment of 1-phenylethanol (**1a**) with 2 equiv of benzyl alcohol (**2a**) in dioxane in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$ (5 mol %) and KOH at 80 °C for 40 h afforded 1,3-diphenylpropan-1-ol (**3a**) in 18% isolated yield with concomitant formation of 1,3-diphenylpropan-1-one (**4a**) (7% yield). Performing the reaction for a longer time (120 h) gave at most a slightly increased yield of **3a** (21%) and **4a** (18%). However, interestingly, when 5 equiv of 1-dodecene was further added, the reaction rate was dramatically enhanced and the secondary alcohol **3a** was obtained nearly as the sole product (**3a**, 82%; **4a**, 3%).

As to the reaction pathway,[11] it seems to proceed via initial oxidations of both substrates to acetophenone (**5**) and benzaldehyde (**6**), respectively (Scheme 2).[12] **5** and **6** then undergo a cross-aldol reaction under KOH to give the α,β-unsaturated ketone **7**, which is subsequently hydrogenated to **4a** and **3a**.[13] Reaction rate enhancement by the addition of 1-dodecene seems to be considered as a faster regeneration of [Ru] from $[Ru]H_2$ generated in the initial oxidation stages by reducing 1-dodecene to dodecane. Thus, forward oxidation is accelerated in the ruthenium-catalyzed redox shuttle, since **5** and **6** are consumed in the aldol reaction. However, unfortunately, an attempt by GLC analysis to detect dodecane in the crude mixture met with failure, since the 1-dodecene and dodecane peaks are exactly eclipsed. Thus, we examined another sacrificial hydrogen acceptor to determine the fate of 1-dodecene. With diphenylacetylene, although the additive effect was lower than that when 1-dodecene was used (**3a**, 32%; **4a**, 23%), we confirmed the reduced species *trans*- and *cis*-stilbene (49% yield based on diphenylacetylene).[14,15] In addition to the usual transfer hydrogenation of **7** to **4a** and **3a** by the starting alcohols **1a** and **2a**, this reaction seems to occur partially by transfer hydrogenation from solvent dioxane. In a separate experiment, we confirmed that **7** was reduced to **4a** and **3a** in 34% and 32% yields, respectively, under the employed conditions $RuCl_2(PPh_3)_3$−KOH−dioxane. It is known that dioxane has been used as a hydrogen donor in transition-metal-catalyzed transfer hydrogenation.[16]

The present reaction could also be applied to many secondary alcohols **1** and primary alcohols **2** (Table 1). The reaction of **1a** with various straight and branched primary alcohols **2a**−**j** gave the corresponding coupled carbinols **3a**−**j** in yields of 70−89%. In all cases, coupled ketones were formed in less than 10% yield. However, no β,β-dialkylation was observed in the GLC and ^{1}H NMR analyses. Similar treatment of 1-phenyl-1-propanol with **2a** under the employed conditions gave no alkylation products. 1-Arylethanols **1b**−**g** were also

Table 1. Ruthenium-Catalyzed β-Alkylation of Secondary Alcohols 1 with Primary Alcohols 2[a]

secondary alcohol **1**	primary alcohol **2**	product **3**	yield[b] (%)
			
1a Ar = Ph	**2a** R = Ph	**3a**	82
	2b R = Pr	**3b**	75
	2c R = pentyl	**3c**	80
	2d R = *i*Bu	**3d**	82
	2e R = *i*Pr	**3e**	76
	2f R = *s*Bu	**3f**	76[c]
	2g R = 3-pentyl	**3g**	70
	2h R = phenethyl	**3h**	78
	2i R = 1-naphthyl	**3i**	89
	2j R = ferrocenyl	**3j**	81
1b Ar = 2-MeC_6H_4	**2a**	**3k**	60
1c Ar = 3-MeC_6H_4	**2a**	**3l**	80
1d Ar = 4-MeC_6H_4	**2a**	**3m**	79
1e Ar = 4-$MeOC_6H_4$	**2a**	**3n**	70
1f Ar = 4-FC_6H_4	**2a**	**3o**	66
1g Ar = 2-naphthyl	**2a**	**3p**	65
	2b	**3q**	90
	**2h**		34
1h		**3r**	
	**2h**		58
1i		**3s**	
	**2h**		25
1j		**3t**	
			
1k	**2a**	**3u**	54[d]
	2b	**3v**	49[e]

[a] Reaction conditions: **1** (1 mmol), **2** (2 mmol), $RuCl_2(PPh_3)_3$ (5 mol %), 1-dodecene (5 mmol), KOH (3 mmol), dioxane (2 mL), 80 °C, for 40 h. [b] Isolated yield based on **1**. [c] Mixture of diastereoisomers (1:0.9). [d] Mixture of diastereomers (5.8:4.2). 2-Benzyl-1-tetralone was also isolated in 30% yield. [e] Mixture of diastereomers (7:3). 2-Butyl-1-tetralone was also isolated in 43% yield.

(11) Santosh Laxmi, Y. R.; Bäckvall, J.-E. *Chem. Commun.* **2000**, 611.
(12) It is known that initial oxidation proceeds via oxidative addition of the O−H bond to Ru and subsequent β-hydrogen elimination.[10]
(13) Bases are used as promoters in transition-metal-catalyzed transfer hydrogenation of ketones to alcohols.[10]
(14) Blum, Y.; Reshef, D.; Shvo, Y. *Tetrahedron Lett.* **1981**, *22*, 1541.
(15) However, treatment of diphenylacetylene under the employed conditions scarcely afforded stilbenes. This result indicates that diphenylacetylene is converted to stilbenes by transfer hydrogenation from the starting alcohols **1a** and **2a**.
(16) (a) Imai, H.; Nishiguchi, T.; Fukuzumi, K. *J. Org. Chem.* **1976**, *41*, 665. (b) Anwer, M. K.; Sherman, D. B.; Roney, J. G.; Spatola, A. F. *J. Org. Chem.* **1989**, *54*, 1284.

reacted with **2a** to afford the coupled carbinols **3k**−**q**, and the product yield was not considerably affected by the position and electronic nature of the substituent on the aromatic ring of **1**. With alkyl methyl carbinols **1h**−**j**, although the product yield was lower than that in the case of aryl methyl carbinols, the alkylation took place exclusively at the less-hindered methyl position over β-methylene and -methine. The reaction of α-tetralol (**1k**) with **2a**,**b** gave not only the corresponding alkylated alcohols (**3u**,**v**) as diastereoisomeric mixtures but also higher yields of alkylated ketones (2-benyl-1-tetralone, 30% yield; 2-butyl-1-tetralone, 43% yield) compared with that when aryl methyl and alkyl methyl carbinols were used.

In summary, we have discovered a novel regioselective β-alkylation of secondary alcohols with primary alcohols in the presence of a catalytic amount of a ruthenium catalyst and KOH along with 1-dodecene as sacrificial hydrogen acceptor. To the best of our knowledge, the present protocol is the first one-pot strategy for β-alkylation of secondary alcohols.

Experimental Section

General Considerations. The ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Bruker Avance Digital 400 spectrometers using TMS as an internal standard. Chemical shifts are reported in δ units downfield from TMS. Melting points were determined on a Thomas Scientific capillary melting point apparatus and were uncorrected. The GLC analyses were carried out with a Shimadzu GC-17A instrument equipped with a CBP10-S25-050 column (Shimadzu, fused silica capillary column, 0.33 mm × 25 m, 0.25 μm film thickness) using nitrogen as the carrier gas. The isolation of pure products was carried out via column chromatography (silica gel 60, 70−230 mesh, Merck) and thin-layer chromatography (silica gel 60 GF254, Merck). Secondary alcohols **1b**−**g** were prepared by reduction of the corresponding ketones with $LiAlH_4$. Commercially available organic and inorganic compounds were used without further purification.

Typical Procedure for Ruthenium-Catalyzed β-Alkylation of Secondary Alcohols with Primary Alcohols. 1a (0.122 g, 1 mmol), **2a** (0.216 g, 2 mmol), 1-dodecene (0.842 g, 5 mmol), KOH (0.168 g, 3 mmol), $RuCl_2(PPh_3)_3$ (0.048 g, 0.05 mmol), and dioxane (2 mL) were placed in a 5 mL screw-capped vial and allowed to react at 80 °C for 40 h. The reaction mixture was filtered through a short silica gel column (EtOAc). Removal of the solvent left an oil, which was separated by thin-layer chromatography (ethyl acetate−hexane 1:10) to give 1,3-diphenylpropan-1-ol (**3a**) in 82% yield. Spectroscopic data for **3a**−**h**,**q**−**t**,**v** are noted in our recent report.[9a]

3-(1-Naphthyl)-1-phenylpropan-1-ol (3i): pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05−2.23 (m, 3H), 3.00−3.07 (m, 1H), 3.14−3.22 (m, 1H), 4.69 (dd, J = 7.8 and 5.3 Hz, 1H), 7.23−7.36 (m, 7H), 7.40−7.45 (m, 2H), 7.67 (d, J = 8.0 Hz, 1H), 7.79−7.81 (m, 1H), 7.92−7.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.0, 39.7, 74.0 (*C*HOH), 123.7, 125.4, 125.5, 125.7, 125.8, 125.9, 126.6, 127.6, 128.4, 128.7, 131.8, 133.8, 137.9, 144.4; MS *m*/*z* (relative intensity) 262 (M^+, 39), 142 (100).

3-Ferrocenyl-1-phenylpropan-1-ol (3j): reddish yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87−2.07 (m, 3H), 2.28−2.35 (m, 1H), 2.41−2.48 (m, 1H), 4.03−4.06 (m, 9H), 4.66 (dd, J = 7.3 and 5.8 Hz, 1H), 7.26−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 39.9, 67.1, 67.8, 68.0, 68.4, 74.1, 88.4, 125.9, 127.5, 128.4, 144.6; MS *m*/*z* (relative intensity) 320 (M^+, 100), 121 (29).

1-(2-Methylphenyl)-3-phenylpropan-1-ol (3k): pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91−2.07 (m, 3H), 2.20 (s, 3H), 2.66−2.73 (m, 1H), 2.78−2.85 (m, 1H), 4.87 (dd, J = 8.0 and 4.5 Hz, 1H), 7.08−7.28 (m, 8H), 7.46 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 32.2, 39.4, 69.8 (*C*HOH), 125.1, 125.8, 126.2, 127.1, 128.3, 128.4, 130.3, 134.4, 141.7, 142.7.

1-(3-Methylphenyl)-3-phenylpropan-1-ol (3l): pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93−2.16 (m, 3H), 2.33 (s, 3H), 2.59−2.75 (m, 2H), 4.58 (dd, J = 7.5 and 5.5 Hz, 1H), 7.05−7.27 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 32.0, 40.3, 73.8 (*C*HOH), 122.9, 125.7, 126.5, 128.25, 128.28, 128.30, 128.4, 138.0, 141.8, 144.5.

1-(4-Methylphenyl)-3-phenylpropan-1-ol (3m): pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96−2.03 (m, 2H), 2.06−2.15 (m, 1H), 2.33 (s, 3H), 2.59−2.75 (m, 2H), 4.59−4.63 (m, 1H), 7.13−7.27 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 32.0, 40.3, 73.6 (*C*HOH), 125.8, 125.9, 128.3, 128.4, 129.1, 137.2, 141.5, 141.8.

1-(4-Methoxyphenyl)-3-phenylpropan-1-ol (3n): pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94−2.03 (m, 2H), 2.07−2.16 (m, 1H), 2.58−2.74 (m, 2H), 3.78 (s, 3H), 4.59−4.62 (m, 1H), 6.86−6.88 (m, 2H), 7.13−7.18 (m, 3H), 7.22−7.28 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.1, 40.3, 55.2, 73.4 (*C*HOH), 113.8, 125.8, 127.2, 128.3, 128.4, 136.7, 141.8, 159.0.

1-(4-Fluorophenyl)-3-phenylpropan-1-ol (3o): pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92−2.01 (m, 1H), 2.04−2.13 (m, 2H), 2.58−2.74 (m, 2H), 4.61−4.64 (m, 1H), 7.00 (t, J = 8.5 Hz, 2H), 7.15−7.19 (m, 3H), 7.22−7.29 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.9, 40.5, 73.1 (*C*HOH), 115.2 (d, J = 21.3 Hz), 125.9, 127.5 (d, J = 7.7 Hz), 128.36, 128.38, 140.2 (d, J = 2.9 Hz), 141.5, 162.1 (d, J = 244.4 Hz).

1-(2-Naphthyl)-3-phenylpropan-1-ol (3p): white solid; mp 61−62 °C (hexane) (lit.[17] mp 64 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01−2.23 (m, 3H), 2.62−2.78 (m, 2H), 4.80 (dd, J = 7.6 and 5.5 Hz, 1H), 7.16−7.20 (m, 3H), 7.24−7.28 (m, 2H), 7.43−7.48 (m, 3H), 7.73 (s, 1H), 7.78−7.82 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.0, 40.3, 73.9 (*C*HOH), 124.0, 124.6, 125.8, 126.1, 127.6, 127.9, 128.31, 128.35, 128.41 (×2), 132.9, 133.2, 141.7, 141.8.

2-Benzyl-1,2,3,4-tetrahydronaphthalen-1-ol (3u): white solid as a diastereoisomeric mixture, the isomeric ratio (5.8:4.2) was determined from the peak areas of the −*C*HOH group in the ^{13}C NMR spectrum; ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.9 (major isomer), 69.3 (minor isomer).

2-Benzyl-1,2,3,4-tetrahydronaphthalen-1-one: pale yellow viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72−1.82 (m, 1H), 2.06−2.13 (m, 1H), 2.63 (dd, J = 13.5 and 9.5 Hz, 1H), 2.70−2.77 (m, 1H), 2.84−2.97 (m, 2H), 3.49 (dd, J = 13.6 and 4.0 Hz, 1H), 7.19−7.23 (m, 4H), 7.28−7.31 (m, 3H), 7.44 (t, J = 7.4 Hz, 1H), 8.07 (d, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 28.5, 35.6, 49.4, 126.1, 126.5, 127.5, 128.3, 128.7, 129.2, 132.4, 133.2, 140.0, 144.0, 199.3 (C═O).

2-Butyl-1,2,3,4-tetrahydronaphthalen-1-ol (3v): pale yellow oil as a diastereoisomeric mixture, the isomeric ratio (7:3) was determined from the peak areas of the clearly separated methine protons in the ^{1}H NMR spectrum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (d, J = 7.0 Hz, C*H*OH, minor isomer), 4.63 (s, C*H*OH, major isomer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.0 (*C*HOH, major isomer), 73.3 (*C*HOH, minor isomer).

Acknowledgment. C.S.C. gratefully acknowledges the Research Professor Program of Korea Research Foundation (Grant No. KRF-2001-050-D00015).

OM030307H

(17) Williams, H. J. *Tetrahedron Lett.* **1975**, *15*, 1271.